REMARKS / ARGUMENTS

Claim Amendments

By the present amendment, claim 49 has been amended. Claims 49, 50 and 78 are currently pending in the present application.

The amendments to the claims have been made without prejudice and without acquiescing to any of the Examiner's objections. The Applicants reserve the right to file any of the canceled subject matter in a divisional patent application. The Applicants submit that no new subject matter has been added by way of the present amendment and entry of the claim amendments is respectfully requested.

The Office Action dated August 7, 2008 has been carefully considered. It is believed that the claims submitted herewith and the following comments represent a complete response to the Examiner's rejections and place the present application in condition for allowance. Reconsideration is respectfully requested.

Claim Rejections

35 USC § 102(b)

The Examiner has maintained the rejection of claims 49-50 pursuant to 35 USC § 102(b) as being anticipated by Denefle et al (WO02/46458) and further by Brennan (US Patent 5,474,796). More specifically, the Examiner notes that the recitation of "shown in" in claim 49 broadly encompasses any nucleic acid fragment. The Examiner has noted that amending claim 49 to recite "the nucleic acid sequences consisting of" will overcome the rejection.

The Applicant has amended claim 49 as suggested by the Examiner.

In light of the foregoing, the Applicant respectfully requests that the rejection to claims 49 and 50 pursuant to 35 U.S.C. § 102(b) be withdrawn.

35 USC § 103(a)

The Examiner has rejected claims 49, 50, and 78 pursuant to 35 USC §103(a) as being unpatentable over Denefle et al. (WO02/46458) in view of Dean et al; Monahan et al; Schmitz (WO00/18912); GenBank AC069137.6; Boyd et al; GenBank U63970.1; Wan et al; Kruh et al; GenBank Z31010.1; and Ota et al. as set out on pages 5 to 9 of the Office Action.

More specifically, the Examiner is of the opinion that it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to use the sequences taught in the prior art cited by the Examiner in the array taught by Denefle et al. The Examiner also stated that the rejection of claims 49 and 50 is drawn to the interpretation that the claims require sequences comprising SEQ ID NO 12, 15, 21, 22, 23, 24, 25, 26, 35 and 44.

As previously noted, claim 49 has been amended to recite "the nucleic acid sequences consisting of..." To the extent that this does not overcome the Examiner's objections under 35 USC § 103(a), the Applicant respectfully disagrees for the reasons that follow.

First, the Examiner states that designing probes, which are equivalent to those taught in the art, is routine experimentation and that the prior art teaches the parameters and objectives involved in the selection of oligonucleotides that function as probes. The Examiner also suggests that there are many internet web sites that provide software that aid in the selection of probes, and that the prior art is "replete with guidance and information necessary to permit the ordinary artisan in the field of nucleic acid detection to design probes".

In response, the Aplicant notes that the claims of the present application are directed towards nucleic acid sequences between 488 and 810 nucleotides in length that are capable of simultaneously distinguishing between members of the ATP-binding cassette (ABC) transporter gene family. While the prior art may teach parameters and objectives involved in the selection of primers and provide software for the selection of relatively short oligonucleotides such as primers, the prior art does not teach the necessary information that

would allow a person skilled in the art to identify the specific nucleic acid sequences found in present claims 49 and 78. Identifying oligonucleotide primer sequences suitable for amplifying a given DNA sequence is not the same as identying a combination of probe sequences each of which is capable of distinguishing members of a particular gene family. The Applicant is not aware of any computer programs in the prior art to design combinations of probes that would result in the identification of the specific sequences found in claims 49 and 78. The claims of the present application are not directed towards individual oligonucleotides, but rather a combination of sequences that each specifically hybridize to one ABC transporter gene.

While the design of primers to amplify an already specified sequence may be considered routine and suggest a reasonable expectation of success, the design of a set of probes is both fortuitous and requires the use of skill and extensive experimental verification. This is especially true for the sequences of the present application, namely the ABC gene family of transporters.

It is clear from the prior art that that all of the 48 known human genes encoding ABC transporters have been cloned and sequenced and that the members of the ABC gene family are similar in sequence and organization. For example, Denefle et al note in paragraph 5:

> "Analysis of amino acids sequence alignments of the ATP-binding domains has allowed the ABC genes to be separated into sub-families (Allikmets et al., Hum Mol Genet, 1996, 5, 1649-1655). Currently, according to the recent HUGO classification, seven ABC gene sub-families named ABC (A to G) have been described in the human genome (ABC1, CFTR/MRP, MDR, ABC8, ALD, GCN20, OABP) with all except one (OABP) containing multiple members. For the most part, these sub-families contain genes that also display considerable conservation in the transmembrane domain sequences and have similar gene organization."

The prior art also refers to the difficulties associated with designing probes suitable for arrays that allow for the unique identification of genes from within gene families. The ordinary artisan would have been aware that cross-hybridization of probe sequences from one member of a gene family to another would lead to spurious results in array experiments.

More recently, the problem of microarray cross-hybridization was discussed in Chen et al. (*A multivariate prediction model for microarray cross-hybridization.* BMC Bioinformatics. 2006; 7: 101) which states on page 2:

> "Cross-hybridization can be a significant contributor to false-positive noise in array data and is known to happen in both oligo and cDNA microarray platforms. Duplex stabilities and re-association kinetics for nucleic acid hybridization is complex, and many factors are involved. Experimental conditions such as hybridization temperature, salt concentration, viscosity of the solvents, pH value are important. Concentration, complexity, lengths, and GC contents, as well as the secondary structures of nucleic acids are also critical. A comprehensive review can be found in [Ptijssen, P. Laboratory Techniques in Biochemistry and molecular biology: hybridization with nucleic acid probes Part I: theory and nucleic acid preparation. Vol. 24. Amsterdam, The Netherlands, Elsevier Science Publishers BV; 1993. Overview of principles of hybridization and the strategy of nucleic acid probe assays; pp. 19–78.].

The prior art therefore teaches that the design of probe sets is complex and is dependent on a number of factors. Moreover, the number of possible probes based on the 10 prior art sequences for ABC-transporter genes identified by the Examiner is virtually infinite. In *KSR*, the Court noted that "[w]hen there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the know options within his or her grasp" (*KSR v. Teleflex* 127 S. Ct. 1727 (2007) at 1732 (Applicant's emphasis)). Here, there is nothing in the prior art to narrow the large number of possible probe sequences to a finite number of identified, predictable solutions. Furthermore, in contrast to the decision in *Pfizer, Inc. v. Apotex*, Inc., this is a case where there are "numerous parameters" to try and is not merely "analogous to the optimization of a range or other variable within the claims that flows from the "normal desire of scientists or artisans to improve upon what is already known"' (see *Pfizer, Inc. v. Apotex*, Inc. CAFC 480 F.3d 1348 at paragraphs 65 and 69,). The Applicant's discovery of a set of nucleic acid sequences that specifically hybridize to only one of the ABC transporter genes simply cannot be characterized as the optimization of a range or other variable through routine experimentation.

The Applicant draws the Examiner's attention to page 35 of the published PCT application, which states:

> "The sets of primers were designed such that the amplification product is a PCR amplicon that is a unique portion of an ABC transporter gene (See table 1).
>
> Figures 1 to 47 show nucleic acid sequences for each PCR amplicon. The primers are shown in bold.
>
> The NCBI (www.ncbi.nim.nig.gov) and BCM search launcher (www. searchlauncher. bcm.tme.edu) websites were used to verify PCR primer identity with the ABC transporter gene region of interest. BLAST sequence searches and alignment analyses were completed for each PCR primer pair and PCR amplicon to ensure minimum cross-hybridization with other known genes and other known ABC transporter genes."

Notably, the Applicants first designed and identified suitable gene regions of interest in order to identify the combination of sequences claimed in the present application. Known methods and computer programs were used to merely verify PCR primer identity with the ABC transporter gene regions of interest. The Applicant also reminds the Examiner that patentability may not be negated by the manner in which the invention was made (35 USC 103).

The Examiner is also of the opinion that the artisan would have been motivated to combine the nucleic acid sequences taught in the prior art because Dean et al teaches ABC gene transporters are important and known to play a role in many diseases, thus determining expression would allow better diagnosis. With respect, it is unclear how the known role of ABC gene transporters in disease would motivate an artisan to combine the specific sequences as claimed in the present application other than at the most general level.

The Examiner further states that the substitution or addition of the sequences taught in the prior art in the arrays taught by Denefle would produce a microarray with probes equivalent to the recited SEQ ID NO by replacing or adding known ABC transporter gene sequences for another. The Examiner is also of the opinion that the artisan would have a reasonable expectation of success as methods of synthesizing nucleic acids and making arrays, as well as the sequences of ABC transporter genes were known at the time of the invention.

As previously noted, the number of possible probes based on the known ABC transporter gene sequences is virtually infinite. Furthermore, there is no clear teaching in the prior art nor a simple variable to optimize that would direct a skilled artisan to produce the specific sequences claimed in the present application by merely replacing or adding known ABC transporter sequences for another. While the sequences of ABC transporter genes, methods of synthesizing nucleic acids and making arrays may have been known at the time of the invention, the Applicant maintains that the differences between the subject matter as a whole and the prior art would not have been obvious to a person having ordinary skill in the art at the time the invention was made.

In view of the foregoing, the Applicant respectfully requests that the rejection to claims 49, 50 and 78 pursuant to 35 USC § 103 be withdrawn.

Early and favorable action on the merits is awaited. Should the Examiner deem it beneficial to discuss the application in greater detail, the Examiner is invited to contact Patricia Folkins by telephone at (416) 957-1683 at the Examiner's convenience.

The Commissioner is hereby authorized to charge any deficiency in fees or credit any overpayment to our Deposit Account No. 02-2095.

Respectfully submitted,

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